ON THE VALUE OF AUTOGENOUS VACCINE THERAPY IN OTITIS FOLLOWING SCARLATINA, WITH NOTES ON THE VACCINE TREATMENT OF OTHER SCARLATINAL SEQUELAE.

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The relationship between Bacteria and Disease has long engaged the attention of the physician, and during the last three decades great progress has been made towards the elucidation of difficulties which from time immemorial have proved stumbling blocks to the advancement of medical science. With the advent of a new era, the Pathologist has become Bacteriologist, and the Clinician has of necessity acquired at least a smattering of both his brothers' sciences.

In the department of Infectious Diseases, perhaps more than in any other has the old order changed - mutatis mutandis -, and given place to a new era characterised by progress. The Etiology of this great section of diseases remained in obscurity, and not until the pilot discovery of the Bacillus Typhosus by Eberth in 1880 was there a break in the horizon. Since then the clouds have scattered somewhat, and although they/

they are by no means yet dispersed, we now view the dragon Disease in the discerning light of knowledge, and are the better able to direct our attacks into channels where it seems vulnerable.

To Diphtheria has been assigned an organism with well defined recognisable specific characters; the complete life cycle of the Malarial Protozoon is now known. Much valuable information has been acquired respecting many of the tropical diseases, but the exact etiology of some of the more common diseases epidemic in our own country remains obscure. Of the causes of Measles and Typhus we know nothing, of Chicken-pox and Small-pox we know little more, while Scarlet fever although generally regarded as in some way connected with Streptococcal infection, has not been definitely proved to result from that cause.

Klein in 1885, Kurth in 1891, Babinsky[1] in 1900 and more recently Mervin Gordon and other investigators have practically accepted a streptococcus as the causal micro-organism, while on the other hand we have such eminent authorities as Class[2] attributing Scarlet fever to a diplococcus, and Mallory, to a protozoon. Class and some others claim to have produced by inoculation in mammals a disease clinically resembling Scarlatina, although Flexner[3] in his recent extended investigations entirely failed to produce symptoms in the lower monkeys. Contacuzène[4] in a publication in May 1911, apparently showed that some of the lower apes are susceptible to the scarlatinal virus, but his results are open to question, in so far as he relied more on fever and glandular enlargement as signs than on the more pathognomonic factors of rash and sore throat. The blood with which he carried on his inoculation experiments was free from streptococci. More recent investigations seem to show that/

that sore throat and definite desquamation can be produced in ourang-outangs, and in many medical circles the trend of opinion is towards accepting the hypothesis first formulated by Bernhardt, that Scarlet fever is due to the superposition of a microbic infection (streptococcal) on an ultra-microscopic filterable virus.

Our lack of definite knowledge concerning the essential cause of Scarlet fever is certainly a very disturbing factor, but be this as it may, there is no doubt many of its worst symptoms and sequelae are due to Streptococci.

Streptococci can frequently be recovered from the urine in cases of albuminuria, and practically always from the faucial secretion during the acute stage. In Rhinorrhoea, they are present in the discharge, although the bacterial flora in this complication is very varied and usually includes diphtheroid organisms and Staphylococci.

Streptococci/

Streptococci and Staphylococci are present in the exfoliating epidermis, while in cases of otorrhoea, streptococci have been present in 68% of the cases which have come under my notice, frequently associated, it is true, with Staphylococci In the numerous superficial septic foci, which are so common in Scarlet fever during convalescence, e.g. paronychia boils, small abscesses, excoriations about the nostrils, face, and scalp, streptococci are occasionally found, although it must be admitted that in those conditions Staphylococci are more prevalent. In three cases where deep seated abscess arose without apparent cause, streptococci were isolated from the pus.

It is a well recognised fact, that, (persistent aural and nasal discharges excepted) the above mentioned complications although in themselves comparatively trivial, are the usual reasons for detention of Scarlet fever patients in hospital beyond the prescribed period. The treatment

of/

of these sequelae by ordinary methods is very protracted, and aural and nasal discharges frequently persist for many weeks in spite of the careful observance of surgical cleanliness and the administration of the most approved medicinal remedies.

Such Scarlatinal complications therefore, in view of their indifferent response to ordinary methods of treatment, offer a wide field for the practice of vaccine therapy, but the varied nature of the conditions, and the frequent difficulty in identifying the causal organism in a mixed growth, combined with the idiosyncrasies of patients as regards dosage, account no doubt for some of the failures which are so apt to dishearten the young vaccine therapist.

It is with Scarlatinal otorrhoea in particular that this paper is intended to deal, and the observations it contains are based on the vaccine treatment of 25 cases in the/

the City of Glasgow Fever Hospital, Belvidere, during 1912.

The frequency of ear complications varies considerably. Finlayson found otitis present in ten per cent of 4397 cases, Caiger in eleven per cent of 4015 cases and Claud Ker in twelve per cent of 5000 cases. Recent statistics in Glasgow show a much smaller percentage (occasionally as low as 5 or 6 per cent) while in Manchester again the frequency rate has greatly increased, not uncommonly attaining the high figure of 20 per cent. During the period dealt with in this paper otitis occurred in 63 out of a total of 873 cases personally observed or 7.2 per cent. In 21 per cent of the affected cases both ears were involved.

Trousseau in his classical description of Scarlatina makes passing mention only of the condition, and most writers while enlarging on the dangers of otitis as liable to open up a path of infection to the meninges say very little regarding its treatment.

In most of the cases Otorrhoea appeared within three weeks of the onset of the fever. In septic cases it not infrequently showed itself during the first week. Occasionally it did not occur until late in convalescence.

The discharge itself varied in character: frequently it was serous, and in three or four cases blood stained. Occasionally its serous character was maintained until its cessation, but sometimes it was purulent from the first.

Pain was also a variable factor in the cases of Otitis observed. Careful investigation of many cases revealed the fact that in adults and children over three years of age, pain (usually accompanied by local tenderness) was a well marked feature, while children under three years of age rarely evinced any localising sign whatever.

Of the prodromata, a sharp rise in temperature of from one/

one to three degrees Fahrenheit and slight increase in pulse rate were found to be the most reliable signs, and in young children even these symptoms were sometimes absent, and the first indication of otitis afforded, was the commencement of the discharge. Even when careful four hourly records of pulse and temperature are kept, and where the child is under constant observation, it is not always easy to anticipate the impending otorrhoea. Many authorities, including Nothnagel, insist that pain is a constant symptom. The writer's own observations do not accord with this statement, indeed they rather suggest that there exists a variety of Otitis - Sine dolore -, in as much as in the present series of cases, pain was rarely evident in young children. Hippocrates, in discussing prognosis says "he is the best physician who knows before hand what is going to happen", but even Trousseau admits that "Scarlatina presents complications which/

which for the most part cannot be foreseen even when they are imminent.

Undoubtedly careful observations enable the physician to anticipate many cases of otorrhoea, but while this is so, it would appear, that a certain number of cases remain where no amount of clinical experience nor exactness in scrutiny avail.

In cases where any suspicion of Otitis exists examination of the membrana tympani affords the best clue to the condition. Its appearance prior to perforation is somewhat uniform:-

Its surface seems flattened, and occasionally is seen to bulge outwards: the handle of the malleus may be obscured and even its short process is sometimes difficult to locate. The membrane itself is usually injected: sometimes it appears opaque and lustreless, and occasionally yellowish in/

in colour due to pus shining through from behind. In a considerable proportion of the cases (all young children) discharge was the first indication of the affection, so that the condition of the membrane prior to the occurrence of perforation was not ascertained. If the membrane be divided into quadrants, the most usual site of perforation is one or other of the lower two, more frequently the posterior than the anterior. As a rule the aperture is of small diameter, but the discharge, even when purulent, and in some degree tenacious, appears to find ready exit.

Fortunately, it matters little so far as treatment is concerned, whether we are able or not to anticipate the advent of otitis, as if routine measures be adopted to secure so far as possible surgical cleanliness of the ears, little further can be done. In spite of the fact that Nothnagel, Osler and McCrae, and others advocate early incision of the membrane, it is found in practice that no harm results, and that/

that rarely does any degree of deafness ensue as the result of pathological perforation of the membrane, provided the process be not too protracted.

What then is the best and most effective method of dealing with aural discharges? The number of cases where the opportunity for treatment of any kind arises previous to perforation is extremely small, and in any event, the disease rarely proves abortive, no matter what measures be adopted. Prior to the commencement of the discharge, several cases under review were tried with stock vaccines of streptococci alone, and combined with staphylococci, without obvious benefit, as in each instance perforation resulted. For the most part, all that can be done at this early stage of the condition is to allay pain with external applications of heat or cold, and to make use of some soothing antiseptic instillation, such as warm almond or olive oil. As a

rule/

rule the physician is called upon to treat otitis cases only after the discharge has made its appearance.

Undoubtedly most cases of otorrhoea consequent upon Scarlatina "clear up" under more or less prolonged treatment with instillations of various antiseptic "ear drops", those which have proved most efficatious in Belvidere Hospital consisting of Hydrogen peroxide, and alcohol in varying dilutions. In the former case 20 to 50 per cent solutions are most satisfactory, while in the latter it is generally advisable to start with 20 per cent Alcohol, and gradually increase the strength until undiluted Spirit. Vini Meth. is used. A solution of iodoform in anilene as recommended by Dr. Albert Gray[6] is a very useful drug in some cases, but has not found favour in routine treatment on account of its great toxicity. If however it be used strictly as recommended there is no danger of any untoward effects.

Insufflation of antiseptics in fine division has been of value, but has the disadvantage of requiring syringing for removal, a practice always to be deprecated as tending to carry infective material onward into channels which are as yet uninvolved. Occasionally it is of advantage to combine these measures with Politserisation and some general tonic treatment, such as the exhibition of small doses of Donovan's solution or Syrup of Iodide of Iron.

Even under the most favourable circumstances, the process of cure by such methods is slow, rarely occupying less than a fortnight, and not infrequently so protracted, as to render the medical attendant very sceptical regarding their efficacy. In fact, no scarlatinal sequela more effectively resists the whole range of artillery of the physician than persistent otorrhoea, but by the addition to his forces of autogenous vaccine therapy he is in possession of a "big gun" which can be used with marked

effect.

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Vide comparison of relative time occupied in treatment by different method. Page 63.

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TECHNIQUE OF PREPARATION OF VACCINES.

The technique of preparation of the vaccines was as follows:-

In most cases immediately discharge was detected, the external ear was carefully cleansed with Hydrogen Peroxide, dried out with 30% alcohol, and plugged with sterile gauze. As soon as there was any recollection, by means of a platinum loop, cultures were taken on agar and in bouillon. In these few cases where the vaccine was not prepared immediately after the detection of the discharge, the same precautions were adopted. In the former a pure culture was frequently obtained; in the latter a mixed growth was the rule. The inoculated tubes were incubated for twenty four hours at 37°C. Slides from each were examined, and if the organism obtained seemed in pure culture, preparation of the vaccine was immediately proceeded with. If a mixed growth resulted, subcultures on agar plateswere prepared in order

to/

to separate the organisms. When streptococci were obtained in combination with any other organisms, the streptococci were selected and the staphylococci or other organisms discarded.

In a few cases pure staphylococcic growths were obtained, and in two cases a polyvalent vaccine was prepared incorporating streptococci and another organism. In three cases also, a mixed vaccine of Staphylococcus aureus along with a short bacillus of the coli group was employed.

It is interesting to note that in several instances the streptococcal growth obtained on agar when examined "in situ" with a low power lens appeared quite typical. In the same growth however when put under the microscope on a slide, chains were often entirely absent, and if present at all were short and atypical, so that the appearance of the field more resembled one of staphylococci than of streptococci. The

bouillon/

bouillon growth in these cases however invariably showed typical long chains. Where possible agar growths were used in the preparation of the vaccines, but in the case of streptococci this was found impracticable on account of the scanty product obtained, and bouillon cultures had to be utilised. Normal saline solution was the agent of dilution employed, and thorough emulsification was secured by agitation for fifteen minutes in the presence of small glass beads. The product was then centrifugalised, using suitable precautions to prevent additional infection, and the emulsion pipetted off, the deposit being discarded. The vaccines were thereafter standardised against normal human blood.

In preparing films it was found that more accurate measurements were obtained by using ordinary capillary tubes in place of Wrights pipettes. One part of bacterial emulsion/

emulsion and one part of blood were usually diluted with several volumes of a 1.5 per cent solution of Sodium Citrate, and in this manner thin and easily counted films were obtained. Three slides were always prepared and stained with Leishman's solution. In each slide fifteen fields were counted and the average of forty five counted fields obtained. From this the strength of the emulsion was calculated. Sterile normal saline was now added until the degree of dilution required for convenient dosage was attained. Sterilisation was ensured by heating for one hour at 54°C. on two separate occasions. In two or three instances it was found that after one hour the vaccine was not sterile, but after two separate hours at 54°C. in no case was a growth obtained. A few minims of a 1 per cent solution of tricresol were added and the vaccines tubed in graduated doses.

Where a pure culture was obtained in the first instance/

instance, the time occupied in the preparation of a vaccine, including the testing for sterility by culture, was from 42 hrs. to 48 hrs. Where mixed growths obtained, and repeated subculturing had to be resorted to, additional time was necessarily required.

Dosage. With regard to dosage no routine scheme was adopted, but on the whole moderate doses were adhered to. In one or two instances massive doses were administered, without enhanced effect. In the case of Staphylococcic vaccines the initial dose was usually from 20 to 50 millions, and it was gradually increased to 500 millions or even 750 millions, although as a rule cure was effected before this latter dose was reached.

Streptococci were given in doses of from 5 millions to 50 millions or even 100 millions.

OPSONIC INDEX. The opsonic index was not estimated in the/

the present series, as previous experience of it in a limited number of ear affections did not seem to afford much guidance as to treatment.

In acute infective processes, especially in streptococcal infections, where auto-inoculation is always taking place, the opsonic content varies greatly even within a few hours, and would require to be estimated every 24 hours to be of any real service. Setting aside discrepancies in results which all but the long experienced must expect, it is obviously impossible, without devoting to it one's entire time, to carry out in a series of cases a process which demands so much conscientious work, and which in the case of certain organisms like the streptococcus is beset with special difficulties.

In practice, the plan adopted answered sufficiently well. Careful observations of pulse and temperature were made/

made where these showed variations from the normal. The general principle that roughly the opsonic index varies inversely with the temperature was adopted, with the result that when a rise in temperature followed an injection of vaccine, an interval of at least four days with normal temperature was allowed to elapse before further dosage. Unfortunately, in many cases, after the first few days, no indication is afforded by pulse or temperature whether to give or withhold an injection, but under these circumstances, the general condition of the patient usually furnishes a clue. If the discharge has increased, or the patient's general condition does not seem so good, it is advisable to wait, whereas, if the sense of well being has increased, or the aural discharge diminished, the time for further dosage is opportune.

It occasionally happens, especially in young children, that the condition shows no appreciable change. Under such circumstances/

circumstances no harm is found to result from increasing graduated doses at intervals of from four to seven days, and generally, the local condition rapidly improves with these measures. Where no reaction follows an injection it may be taken that the dose has not been unduly large, and that cautious increase is called for.

In the undernoted cases the time interval allowed to elapse between doses was usually from four to ten days. Two cases, in which to begin with, injections were repeated every alternate day did not appear to derive additional benefit.

On the other hand, it is worthy of note that in four cases the discharge ceased within 72 hours of the initial dose of vaccine, which seems to indicate that when moderate doses are employed, the negative phase, if it exists at all is of short duration. Probably the explanation of the fact that/

that the above mentioned two cases where injection was repeated every alternate day did no better than the others, does not lie in the establishment and continuance of a negative phase.

CAUSES OF FAILURE. Other causes of failure are not far to seek, and perhaps the most important of them depends on the difficulty in certain cases of selecting the true causal organism. In this connection it is observed, that where a mixed growth is obtained, the tendency is for the streptococcus to be overgrown by the other organisms present, especially where cultures on agar only are used. Moreover, the fact that on this medium streptococcal growths are sometimes atypical, exhibiting in films an appearance much more like staphylococcic growths, favours the conclusion that occasionally a staphylococcus may be accepted as the causal organism, and the presence of the streptococcus which is in reality the "causa causans" overlooked. Inability to isolate the true causal/

causal organism is necessarily attended with failure in the treatment of the case, and no doubt it is to such mishaps that some of our nonsuccesses are due.

In support of the above, I quote the following case, the chart of which is appended.

E VI.
.D.

Aet. 2. admitted 16th Feb., 1912 on 2nd day of illness: a well nourished sturdy female child with sharp attack of scarlet fever. Thoracic and abdominal organs normal. Urine free from albumin. Temperature 103°.6. Pulse 152. Respirations 30.

The course of the illness was severe: the throat was very dirty, and sloughs separated from the tonsils. The buccal mucosa was also deeply ulcerated in places.

By 11th March pulse and temperature had become normal, and the condition of mouth greatly improved. Convalescence proceeded until 10th April when the patient developed a typical reinfection of scarlatina. Temperature 102°4.

Pulse 136. Respirations 28.

Name N. D. Age 2 yrs Disease Scarlatina Index No. VI.

Day of Month	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29
Day of Disease	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73
Hours of Day	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.
Pulse																					
Respiration	20/22	26/28	28/30	26/28	26/28	26/26	26/24	24/24	26/26	24/24	24/24	24/24	24/24	24/24	24/24	24/24	24/24	24/24	24/24	24/24	24/24

F. 107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97°

C 41° 40° 39° 38° 37° 36°

Rash faded

Rash disappearing

April, 1912.

Name N.D. Age 2 yrs. Disease Scarlatina Index No. VI.

Day of Month	30	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Day of Disease	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94
Hours of Day	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.

F. 107° / P. 160. 106° / 150. 105° / 140. 104° / 130. 103° / 120. 102° / 110. 101° / 100. 100° / 90. 99° / 80. 98° / 70. 97°

C 41° 40° 39° 38° 37° 36°

Vaccine (No. 1) 50 m.m. Vaccine (No. 2) 150 m.m. Vaccine (No. 1) 300 m.m. Vaccine (No. 2) 10 m.m. Vaccine (No. 1) 350 m.m. Vaccine (No. 2) 20 m.m.

Pulse

Respiration

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May, 1912.

Name N. D. Age 2yrs. Disease Scarlatina Index N° VI.

Day of Month	21	22	23	24	25	26	27	28	29	30	31	1
Day of Disease	95	96	97	98	99	100	101	102	103	104	105	106
Hours of Day	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.	M.E.
Pulse												
Respiration	24/22	22/22	22/24	20/24	22/22	22/20	20/22	20/22	20/20	22/20	20/20	20/20

Measles (Rash) 28th

Desquamation

F. 107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97°

C 41° 40° 39° 38° 37° 36°

May, 1912.

The chart now indicates the course of the illness. Acute symptoms rapidly subsided and soon convalescence was again satisfactory.

On 28th April, without any rise in temperature or local signs, abundant serous discharge from the left ear commenced. Examination of the membrane showed a small perforation in the posterior inferior quadrant. Cultures on agar only were made and yielded growths of Staphylococcus albus. An autogenous vaccine was prepared and on

1st May an initial dose of 50 millions was given. There was no temperature response, and no improvement in the aural condition.

On 4th May 150 millions, and on 8th May 300 millions were given with the same negative result. Fresh cultures were now taken in bouillon and a streptococcus isolated, from which a second vaccine was prepared.

On 11th May a 10 million dose of Vaccine No. 2. was administered/

administered.

On 13th May the discharge was much diminished, and accordingly a 20 million dose of vaccine No. 2. was given. It was combined with 300 millions of vaccine No. 1. There was a slight temperature response - 99°8 and the quantity of discharge was somewhat increased.

On 17th May the discharge was again greatly reduced in quantity.

On 22nd May the previous dose was repeated and from this date the aural discharge steadily diminished in amount until on 26th May it finally ceased.

Seven days later the perforation had quite healed and hearing seemed unimpaired.

In the above case it would appear that the wrong organism was selected in preparing the initial vaccine, and certainly no benefit resulted from its exhibition. Since agar only was the culture medium used in the first instance/

instance, probably any streptococci present were overgrown by staphylococci: when bouillon cultures were prepared, a streptococcal growth was obtained, and the administration of vaccine No. 2. prepared from it, was marked by almost immediate benefit.

As already stated the majority of cases of Otorrhoea treated proved to be streptococcal infections, while a certain number were undoubtedly staphylococcic in origin. At this stage it may be opportune to give details of some typical examples, before tabulating the series:

Taking streptococcal infections first of all, the following three cases are examples of the type yielding readily to treatment. It is noticeable that in each case the discharge was serous, and generally speaking it was found that such cases yielded to vaccine treatment with greater readiness than those in which the discharge was frankly purulent./